

Claims

1. A peptide, the amino acid sequence of which consists of an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1);
GSLPHSL (SEQ ID NO. 2);
TQLFPPQ (SEQ ID NO. 3);
HSIPDNI (SEQ ID NO. 4);
HHMPHDK (SEQ ID NO. 5);
YTTPPSP (SEQ ID NO. 6); and
QLPLMPR (SEQ ID NO. 7).

2. The peptide of claim 1, wherein the amino acid sequence is selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1); and
TQLFPPQ (SEQ ID NO. 3).

3. A peptide up to 60 amino acids in length comprising an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1);
GSLPHSL (SEQ ID NO. 2);
TQLFPPQ (SEQ ID NO. 3);
HSIPDNI (SEQ ID NO. 4);
HHMPHDK (SEQ ID NO. 5);
YTTPPSP (SEQ ID NO. 6); and
QLPLMPR (SEQ ID NO. 7),

wherein the peptide is capable of binding to Nogo, MAG and/or TN-R.

4. The peptide of claim 3, which comprises the amino acid sequence YLTQPQS (SEQ ID NO. 1) or TQLFPPQ (SEQ ID NO. 3).

5. A peptide up to 60 amino acids in length comprising an amino acid sequence having at least 5 residues identical with

corresponding residues in an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1);
GSLPHSL (SEQ ID NO. 2);
TQLFPPQ (SEQ ID NO. 3);
HSIPDNI (SEQ ID NO. 4);
HHMPHDK (SEQ ID NO. 5);
YTTPPSP (SEQ ID NO. 6); and
QLPLMPR (SEQ ID NO. 7),

wherein the peptide is capable of binding to Nogo, MAG and/or TN-R.

6. The peptide of claim 5, which has at least 5 residues identical with corresponding residues in an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1); and
TQLFPPQ (SEQ ID NO. 3).

7. The peptide of claim 5 or claim 6, wherein the number of identical residues is at least 6.

8. The peptide of any one of claims 3 to 7, which is capable of binding to Nogo-66 and/or TNR-EGFL.

9. The peptide of any one of claims 3 to 8, which is up to 40 amino acids in length.

10. The peptide of claim 9, which is up to 20 amino acids in length.

11. The peptide of claim 10, which is up to 10 amino acids in length.

12. A composition comprising one or more peptides according to any preceding claim, together with one or more pharmaceutically acceptable ingredients.
13. A peptide according to any one of claims 1 to 11 for use in a method of treatment.
14. The use of a peptide according to any one of claims 1 to 11 in the preparation of a medicament for the treatment of CNS damage.
15. A method for treating CNS damage, the method comprising administering a peptide according to any one of claims 1 to 11 to a patient at or near a site of CNS damage in the patient.
16. A method for treating spinal cord injury or stroke, the method comprising administering to a patient a peptide having an amino acid sequence that consists of an amino acid sequence selected from the group consisting of:
- YLTQPQS (SEQ ID NO. 1); and
- TQLFPPQ (SEQ ID NO. 3),
- by direct injection into a site of spinal cord injury or stroke damage in the patient.
17. The use of a peptide according to any one of claims 1 to 11 and/or a computer-generated model thereof, in the design of a mimetic capable of binding to one or more of the neuronal growth inhibitory molecules Nogo, MAG and/or TN-R.
18. A method of designing a mimetic of a peptide as defined in any one of claims 1 to 11, the mimetic being capable of binding to one or more of the neuronal growth inhibitory molecules Nogo, MAG and/or TN-R, said method comprising:

(i) analysing a peptide as defined in any one of claims 1 to 11 that is capable of binding to one or more of the neuronal growth inhibitory molecules Nogo, MAG and/or TN-R to determine the amino acid residues essential and important for the activity to define a pharmacophore; and

(ii) modelling the pharmacophore to design and/or screen candidate mimetics having the biological activity.

19. The use or method of claim 17 or claim 18, which includes a step of assaying binding of a candidate mimetic to Nogo, MAG and/or TN-R in vitro.

20. The use or method of any one of claims 17 to 19, which includes a step, having identified a candidate mimetic that is capable of such in vitro binding, of optimizing the candidate mimetic for in vivo use.

21. The use or method of claim 20, wherein the optimised mimetic is formulated together with one or more pharmaceutically acceptable ingredients.

22. A bacteriophage which expresses a fusion protein consisting of a peptide and a bacteriophage coat protein, such that the peptide is displayed on the surface of the bacteriophage virion, wherein the peptide is as defined in any one of claims 1 to 11.

23. A screening method for peptides capable of binding to Nogo, MAG and/or TN-R, the method comprising:

providing bacteriophages of claim 22, respectively expressing different peptides; and

screening the bacteriophages for the ability to bind to Nogo, MAG and/or TN-R.

24. The method of claim 23, wherein bacteriophages which are identified as being capable of binding to Nogo, MAG and/or TN-R, or the peptides they display, are then be screened for the ability to block the inhibitory effects of Nogo, MAG and/or TN-R on neuronal cell adhesion in an in vitro assay.

25. A method comprising all the steps of claim 24 and an additional step, following the identification of a peptide, or phage that displays a peptide, that is capable of blocking the inhibitory effects of Nogo, MAG and/or TN-R on neuronal cell adhesion in an in vitro assay, of formulating the peptide with one or more pharmaceutically acceptable ingredients for administration in vivo.

26. A method of searching for factors that are likely to reduce the inhibitory effect of TN-R, MAG and/or Nogo, the method comprising interrogating a sequence database to identify polypeptides, or nucleic acids that encode polypeptides, that comprise an amino acid sequence having at least 5 residues identical with corresponding residues in an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1);
GSLPHSL (SEQ ID NO. 2);
TQLFPPQ (SEQ ID NO. 3);
HSIPDNI (SEQ ID NO. 4);
HHMPHDK (SEQ ID NO. 5);
YTTPPSP (SEQ ID NO. 6); and
QLPLMPR (SEQ ID NO. 7).

27. A method of searching for factors that are likely to reduce the inhibitory effect of TN-R, MAG and/or Nogo, the method comprising screening a cDNA library with an oligonucleotide probe which is capable of hybridising under stringent conditions with a nucleic acid sequence that encodes

an amino acid sequence having at least 5 residues identical with corresponding residues in an amino acid sequence selected from the group consisting of:

YLTQPQS (SEQ ID NO. 1);
GSLPHSL (SEQ ID NO. 2);
TQLFPPQ (SEQ ID NO. 3);
HSIPDNI (SEQ ID NO. 4);
HHMPHDK (SEQ ID NO. 5);
YTTPPSP (SEQ ID NO. 6); and
QLPLMPR (SEQ ID NO. 7).

28. The method of claim 26 or claim 27, which includes the step, following the identification of a candidate polypeptide or nucleic acid encoding the candidate polypeptide, of testing the polypeptide for the ability to reduce the inhibitory effect of TN-R, MAG and/or Nogo.

29. A method comprising all the steps of claim 28 and an additional step, following the identification of a polypeptide that is capable of blocking the inhibitory effects of Nogo, MAG and/or TN-R on neuronal cell adhesion in an in vitro assay, of formulating the polypeptide with one or more pharmaceutically acceptable ingredients for administration in vivo.

30. A nucleic acid vector comprising nucleic acid encoding one or more polypeptide domains selected from the group consisting of:

(a) the N-terminal domain (NogoN) of Nogo-A, or a variant or fragment thereof;

(b) the extracellular loop (Nogo66) of Nogo-B, or a variant or fragment thereof;

(c) the third to fifth immunoglobulin-like repeats of MAG, or a variant or fragment thereof; and

(d) the EGF-like domain of TN-R, or a variant or fragment thereof,

wherein said fragment comprises at least 15 contiguous amino acids from said domain, includes one or more epitopes of said domain and retains the ability to raise an antibody response in vivo, and

wherein said variant includes a portion of at least 15 amino acids that has at least 65% amino acid identity to a corresponding portion of said domain.

31. The vector of claim 30, wherein the nucleic acid encodes at least two of the domains.

32. The vector of claim 31, wherein the domains are expressed as a fusion polypeptide.

33. The vector of claim 32, wherein the domains are separated from one another by flexible linkers.

34. The vector of any one of claims 30 to 33 wherein, of the proteins Nogo A, Nogo B, TN-R and/or MAG, the vector is preferably capable of expressing substantially only the domains (a), (b), (c) and/or (d) recited in claim 30.

35. The vector of claim 34, wherein the vector is incapable of expressing other epitope-containing portions of the proteins.

36. The vector of claim 34 or claim 35, wherein, of the proteins Nogo A, Nogo B, TN-R and/or MAG, the vector preferably expresses no more than 20% of the protein lying outside domains (a) to (d) recited in claim 30.

37. The vector of any one of claims 30 to 36, wherein the domain (a) has the amino acid sequence of NogoN (1-185) (SEQ ID NO:10), domain (b) has the amino acid sequence of Nogo66 (823-888) (SEQ ID NO:11), domain (c) has the amino acid sequence of MAG (1-508) (SEQ ID NO:8), and domain (d) has the amino acid sequence of TNR (125-329) (SEQ ID NO:9).

38. The vector of claim 30, which encodes a polypeptide having the amino acid sequence MAG(1-508)-Ala_n-TNR(125-329)-Ala_n-NogoN(1-185)-Ala_n-Nogo66(823-888) (SEQ ID NO:12), where Ala_n represents an polyalanine linker.

39. A composition comprising the vector of any one of claims 30 to 38, formulated together with one or more pharmaceutically acceptable ingredients for use as a therapeutic vaccine.

40. The vector of any one of claims 30 to 38, for use in a method of treatment.

41. Use of the vector of any one of claims 30 to 38 in the manufacture of a medicament for the treatment of CNS damage.

42. A method for treating CNS damage in a patient, the method comprising administering the vector of any one of claims 30 to 38 to the patient as a therapeutic vaccine.

43. A polypeptide consisting essentially of one or more polypeptide domains as defined in claim 30.

44. The polypeptide of claim 43, which is encoded by the vector of any one of claims 30-38.

45. A composition comprising the polypeptide of claim 43 or claim 44, formulated together with one or more pharmaceutically acceptable ingredients for use as a therapeutic vaccine.

46. The polypeptide of claim 43 or claim 44, for use in a method of treatment.

47. Use of the polypeptide of claim 43 or claim 44 in the manufacture of a medicament for the treatment of CNS damage.

48. A method for treating CNS damage in a patient, the method comprising administering the polypeptide of claim 43 or claim 44 to the patient as a therapeutic vaccine.

49. An antibody capable of specifically binding to any one of domains (a)-(d) as defined in claim 37, or a mixture of antibodies together capable of binding to two, three or all four of domains (a)-(d) as defined in claim 37, for use in a method of treatment.

50. Use of an antibody capable of specifically binding to any one of domains (a)-(d) as defined in claim 37, or a mixture of antibodies together capable of binding to two, three or all four of domains (a)-(d) as defined in claim 37, in the manufacture of a medicament for the treatment of CNS damage.

51. A method for treating CNS damage in a patient, the method comprising administering to the patient as a therapeutic vaccine an antibody capable of specifically binding to any one of domains (a)-(d) as defined in claim 37, or a mixture of antibodies together capable of binding to two, three or all four of domains (a)-(d) as defined in claim 37.

52. A composition comprising an antibody capable of specifically binding to any one of domains (a)-(d) as defined in claim 37, or a mixture of antibodies together capable of binding to two, three or all four of domains (a)-(d) as defined in claim 37, formulated together with one or more pharmaceutically acceptable ingredients for use as a therapeutic vaccine.

53. The composition of any one of claims 12, 39, 45 and 52, which is formulated for administration by injection.

54. The peptide of claim 13, the vector of claim 40, the polypeptide of claim 46 or the antibody of claim 49, wherein the treatment is the treatment of CNS damage.

55. The peptide of claim 13, the vector of claim 40, the polypeptide of claim 46 or the antibody of claim 49, wherein the treatment is the treatment of spinal cord injury or stroke.

56. The use of any one of claims 14, 41, 47 and 50, wherein the treatment is of spinal cord injury or stroke.